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Validation of the high mortality rate of Malnutrition-Inflammation-Atherosclerosis syndrome –Community-based observational study–

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ABSTRACT

Background: Malnutrition-Inflammation-Atherosclerosis (MIA) factors significantly and independently affect life prognosis of hemodialysis (HD) patients. We re-evaluated Japanese data, which have progressed ahead from a community-based observational study. The present study was designed to assess the contribution of these MIA factors to the mortality rate of Japanese HD patients in a community of 1.8 million people over a 36-month follow-up period.

Methods and results: A total of 5813 patients at 76 facilities were on maintenance HD in the Kumamoto Prefecture. Specifically, 4807 of these patients at 58 institutions were enrolled. Patients who exhibited lower serum albumin and higher serum C-reactive protein levels were defined as "malnourished" and "inflamed", respectively, compared with the median values. Patients who underwent invasive procedures for atherosclerotic diseases were defined as "atherosclerotic".

The 36-month all-cause mortality rate in Japanese HD patients was 12.4%. This rate directly correlated with the number of MIA factors. The odds ratio of the all-cause mortality rate markedly and significantly increased as the number of factors increased. The presence of 3 MIA factors in HD patients was a significant predictor of mortality, as evidenced by a multivariate logistic regression analysis.

Conclusions: This study clearly demonstrated the close association between MIA syndrome and high mortality in Japanese HD patients. Early detection and the adjustment of MIA factors are mandatory.

1. Introduction

The number of patients with chronic kidney disease (CKD) has explosively increased worldwide, and an increasing number of end-stage renal disease (ESRD) patients on hemodialysis (HD) have been a social problem in Japan [1,2]. In Japan, kidney transplantations were not performed compared to western countries, and ESRD patients generally undergo HD. Because the main cause of death in HD patients is cardiovascular disease (CVD) [3–7], the risk stratification of CVD in these patients might be very important [8]. Recently, Nagata et al. reported that low-density lipoprotein cholesterol levels could not predict major adverse cardiac events in HD patients undergoing percutaneous coronary intervention [9], whether lipid profiles can predict clinical outcomes in HD patients with ischemic heart disease is controversial [10]. Because it may increase in HD patients due to the progress of developing countries, we re-evaluated Japanese data, which has progressed ahead.

Inflammation has been shown to be deeply involved in the progression of atherosclerosis [11,12], and chronic inflammation can also contribute to malnutrition. Inflammation is common in HD patients [13], and increases in the serum C-reactive protein (CRP) levels are consequently an independent risk factor for CVD [14]. CVD and malnutrition are strongly associated in CKD [15], and malnutrition has consequently been proposed as a prognostic factor of CVD. Stenvinkel et al. reported that inflammation and malnutrition are closely associated with arteriosclerosis/CVD, and they have referenced MIA (Malnutrition-Inflammation-Atherosclerosis) syndrome [16]. They stated that inflammatory cytokines played important roles in MIA syndrome and that

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they would be important causes of atherosclerosis and malnutrition. Notably, this syndrome integrates malnutrition, inflammation and atherosclerosis. These 3 components significantly and independently affect the prognosis of HD patients; the mortality rate is significantly and directly associated with the number of MIA factors. Although the mortality rate markedly increases with the number of MIA factors, little is known about the actual odds ratios (ORs) in Japanese patients. We have reported that the mortality rate of peripheral artery disease (PAD) patients was high, despite receiving various invasive cardiovascular procedures (ICPs) after a 12-month follow up of 4807 Japanese patients [17]. The present study was designed to assess the contribution of MIA factors to the mortality rate in Japanese HD patients in a community of 1.8 million people over a 36-month follow-up period.

2. Methods

2.1. Ethical consideration

All procedures will be conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol has been approved by the institutional review board of each institutions and written informed consent will be obtained from each patient or from the family of the patient.

This study follows the STROBE guidelines [18] for observational studies.

2.2. Study design and participant enrolment

This study was a multicenter, prospective, registry study throughout the Kumamoto Prefecture. The Kumamoto Prefecture is located southwest of Tokyo and has a population of approximately 1.8 million people. According to the 2011 official report of The Japanese Society for Dialysis Therapy, 5813 patients at 76 facilities were on maintenance hemodialysis in the Kumamoto Prefecture. Specifically, 4807 of these patients at 58 institutions were enrolled in this study from January to December 2011 [17]. Thus, the registration rate was 76.3% (58/76) for facilities and 82.7% (4807/5813) for patients. The observation time limit was to achieve primary endpoint described below and the patient who had acute renal failure (regular dialysis treatment > 3 months) was excluded.

Table 1A
Baseline patient characteristics at the time of enrolment.

	Death (n = 341)	Survival (n = 2418)	P
Age (years)	75.1 ± 11.7	67.9 ± 13.2	<0.001
Time on HD duration (years)	9.4 ± 8.4	8.5 ± 7.9	0.046
Body height (cm)	157.2 ± 9.8	158.6 ± 9.6	0.021
Body weight before-HD (kg)	52.2 ± 11.7	56.3 ± 11.8	<0.001
BMI before-HD (kg/m^2)	21.1 ± 3.9	22.2 ± 3.5	<0.001
Male (%)	202(59.4)	1426(59.3)	0.974
Hypertension (%)	140(60.6)	1286(72.7)	<0.001
Current smoker (%)	22(9.6)	211(12.4)	0.225
Diabetes mellitus (%)	113(47.1)	769(43.0)	0.235
BUN before HD (mg/dL)	53.9 ± 14.1	60.8 ± 14.8	<0.001
Atherosclerosis history	85(24.9)	383(15.8)	<0.001
Creatinine before HD (mg/dL)	8.2 ± 2.6	9.9 ± 2.6	<0.001
Calcium (mg/dL)	9.0 ± 0.7	9.0 ± 0.8	0.271
Phosphorus (mg/dL)	4.7 ± 1.3	5.1 ± 1.3	<0.001
Albumin (g/dL)	3.4 ± 0.5	3.7 ± 0.4	<0.001
CRP (mg/dL)	1.98 ± 3.92	0.53 ± 1.72	<0.001
Hemoglobin (g/dL)	10.2 ± 1.3	10.5 ± 1.3	0.002
Uric acid (mg/dL)	6.8 ± 1.3	7.4 ± 1.9	<0.001
Total-cholesterol (mg/dL)	150.1 ± 39.3	154.8 ± 35.8	0.070
HDL-cholesterol (mg/dL)	43.3 ± 13.4	46.7 ± 14.6	0.004

HD; hemodialysis, atherosclerosis history; history of atherosclerotic diseases, BUN; blood urea nitrogen, CRP; serum C-reactive protein, HDL; high-density lipoprotein.

We evaluated all-cause mortality during a 36-month follow-up period. We also examined anthropometric measures (e.g., age, sex, body weight, and body height), laboratory test results and medical history. Baseline clinical and laboratory data were obtained from stable patients prior to HD.

The exact observational end date was 31st, December 2014. All data were collected and aggregated by a trained research team at the Division of Cardiovascular Disease of Kumamoto University.

Study flow chart was demonstrated in Fig. 1.

2.3. Endpoint

The study endpoint was all-cause mortality. Ideally the other causes of death (cancer, accidents, etc.) have to be excluded. Originally MIA syndrome was well known to be associated with cardiovascular death.

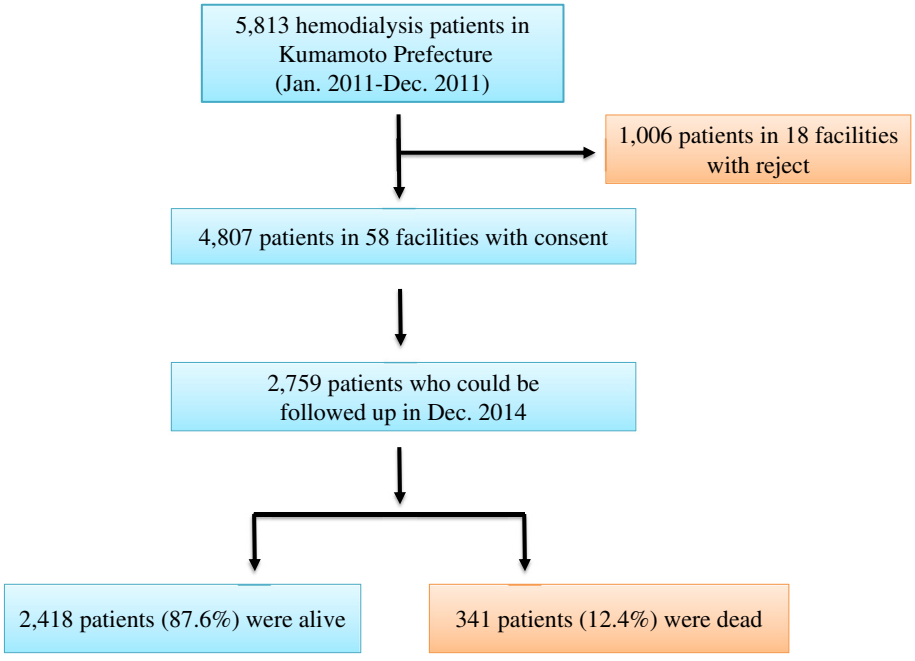

Fig. 1. Study flow chart.